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EXAMINER	
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ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,669	STRITTMATTER ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-61* is/are pending in the application.

4a) Of the above claim(s) *48,50,57, 59 and 61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-47,49,51-56,58 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Election/Restriction filed on June 08, 2007 is acknowledged. Claims 42-61 are pending in this application.

Election/Restriction

1. Applicant's election with traverse of species SEQ ID NO:3 in the reply filed on June 08, 2007 is acknowledged. The traversal is on the ground(s) that each peptide sequence and variants thereof function similarly and contain specific features in their sequences required for that function. Furthermore, the Applicants argue that the species of claims 48, 49, 57 and 58 share both a common utility and substantial structural features essential to that utility, and thus have unity of invention. This is not found persuasive because the species of claims 48, 49, 57 and 58 are patentably independent and distinct. The sequences are structurally different due to different amino acid content. For example amino acid 280-310 of SEQ ID NO:3 is structurally different from SEQ ID NO:5 (i.e., GSSSEVPCSLPQRLAGRDKRLAANDLQGCA vs. GSSSGVPSNLPQRLAGRDLKRLATSDLEGCA). A search for SEQ ID NO:3 would not lead to SEQ ID NO:5, since the sequences are different. This would require independent searches. Further, Claims 48 and 57 recite "up to ten conservative amino acid substitutions". The peptides recited in claims 48 and 57 are patentably independent and distinct because each peptide would have different structures due to conservative amino acid substitutions. Since there are 26 to 310, 26 to 344, 27 to 310, and 27 to 344 amino acids, conservative amino acid substitutions can occur at any amino acids. This

leads to innumerable variables, thus would require independent searches to be conducted. The search for each of the species is not co-extensive particularly with regard to the literature search. Burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement, and double patenting issues. Further, a reference that would anticipate the species of one group would not necessarily anticipate or even make obvious another group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine all of the above inventions in one application and the restriction for examination purposes as indicated above is deemed proper.

2. The requirement is still deemed proper and is therefore made FINAL. Claims 48, 50, 57, 59 and 61 are withdrawn from further consideration as being drawn to nonelected species. Claims 42-47, 49, 51-56 and 59-60 are examined on the merits in this office action.

Objection-Minor Informalities

3. The title is objected to because the title is too long. The title is limited to 2-7 words maximum. A new title is required that is clearly indicative of the invention to which the claims are directed.

4. The specification is objected to because there appears to be a spelling or grammatical error. At paragraph [0016], 5th line, the specification recites "definitions will control". This error should be corrected.

5. The specification is objected to because there appears to be an error at paragraph [0069], line 22. The specification recites "brain AB levels", and throughout the specification, Ab peptide is written as "Aβ peptide". This error should be corrected.

Rejection-35 U.S.C. 112, 2nd

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 45-47 recite the limitation "the soluble Nogo receptor polypeptide" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim, since the specification discloses that Nogo receptor antagonist include soluble Nogo receptor-1 polypeptides, antibodies that bind to the Nogo receptor protein and antigen-binding fragments of such antibodies, an small molecule antagonists (see paragraph [0030]). A soluble Nogo receptor polypeptide appears for the first time in claim 45.

Rejection-35 U.S.C. 112, 1st

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-47, 51-56 and 59-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

9. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

10. Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

11. The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

12. In the instant case, the claims are drawn to a method for reducing the levels of Ab peptide in a mammal comprising administering a therapeutically effective amount of a soluble Nogo receptor antagonist. The generic statement a soluble Nogo receptor antagonist does not provide ample written description for the compounds since the

claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

13. As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 42 is broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule that make up the class of Nogo receptor antagonist. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule or other peptidic molecules and other synthetic peptide or peptide-like molecule that can function as Nogo receptor antagonist.

14. The specification is limited to the peptide or peptide-like molecules that belong to the same class of protein, Nogo receptor antagonist. The specification disclosed that

"Nogo receptor antagonist" means a molecule that inhibits the binding of Nogo receptor-1 to a ligand (e.g., NogoA, NogoB, NogoC, MAG, OM-gp) (see paragraph [0026]). Further, the specification discloses that Nogo receptor antagonist may include soluble Nogo receptor-1 polypeptides, antibodies that bind to the Nogo receptor protein and antigen-binding fragments of such antibodies, and small molecule antagonists (see paragraph [0030]). The working example describes the Nogo receptor-1 polypeptide (both human and rat, SEQ ID NOS: 3-6) (see paragraph [0031]). The specification further discloses that Nogo receptor antagonist that is an antibody or an antigen-binding fragment thereof that specifically binds an immunogenic Nogo receptor-1 polypeptide and inhibits the binding of Nogo receptor-1 to a ligand and these antibodies may be produced in vivo or in vitro, recombinant, engineered, humanized and/or chimeric (see paragraph [0034]). The working example only describes the treatment with sNgR310 (SEQ ID NO:3) fused with immunoglobulin moiety Fc (sNgR310-Fc) to examine the role of NgR/APP/Aβ interaction (see Example 6, paragraph [0069]). The specification does not describe any other Nogo receptor antagonist, such as any other proteins (such as Nogo-66 receptor-related protein 3, GenBank Accession Number Q86UN2), or any other type of peptide or peptide-like molecule that act as Nogo receptor antagonists (such as small organic molecules). Descriptions of SEQ ID NOS: 3-6 and antibodies for Nogo receptor antagonist are not sufficient to encompass numerous other proteins and small molecules that belong to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. As described above, GenBank Accession # Q86UN2, is a Nogo-66 receptor

homolog (also reticulon-4 receptor-like 1 precursor). GenBank Accession Number NP 075358 is a reticulon-4 receptor from the mouse species. This comprises of 473 amino acids in lengths and comprises the same amino acid sequence of SEQ ID NO:3, thus would function as a Nogo receptor antagonist. Further, the specification does not describe any analogs and homologs of Nogo receptor antagonists and a description of peptide with up to 10 conservative amino acid substitution for SEQ ID NOS: 3-6 is not enough to encompass the derivatives. This is because SEQ ID NOS: 3-6 have 284 amino acids, 318 amino acids, 283 amino acids, and 317 amino acids, respectively. There are innumerable possibilities that encompass these conservative amino acid substitutions. Further, the specification does not describe what small molecule would function as a Nogo receptor antagonist. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

15. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

16. Claims 42-47, 49, 51-56 and 59-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to a method for reducing the levels of Aβ peptide in a mammal and a method for preventing or treating a disease, disorder or condition associated with plaques of Aβ peptide in a mammal, comprising administering soluble Nogo receptor antagonist.

(2) The state of the prior art:

In regards to "preventing a disease, disorder or condition associated with plaques of Aβ peptide in a mammal", it is well known in the art that Alzheimer's disease (AD) is associated with plaques of Aβ peptide ($A\beta_{1-40}$ and $A\beta_{1-42}$) in neuritic plaques (see for example, Liu et al, PNAS Early Edition, Feb 2001, 1-6). The Merck manual indicates Alzheimer's disease is chronic, global, usually irreversible deterioration of cognition. The main types of Alzheimer's disease are: vascular dementia, Lewy body dementia, frontal-temporal dementias, and HIV-associated dementia (See Merck manual, "Dementia", Etiology and Classification, 2nd paragraph). Furthermore, Alzheimer's disease causes progressive cognitive deterioration and is characterized by senile plaques, beta-amyloid deposits, and neurofibrillary tangles in the cerebral cortex and subcortical gray matter (see Merck manual in Dementia under "Alzheimer's disease). Furthermore, the Merck manual indicates that most cases are sporadic, with late onset and unclear etiology (see Merck manual, "Alzheimer's disease", Etiology and Pathophysiology). Since symptoms, signs are similar to those of other dementia, distinguishing Alzheimer's disease from other dementias is difficult (see Merck Manual, "Alzheimer's disease", Symptoms, Signs, and Diagnosis).

Furthermore, Mattson MP (Nature, 2004, 430: 631-639) indicates that the risk of Alzheimer's disease (AD) dramatically increases in individuals beyond the age of 70 (see p. 631, left column, 1st sentence). The vast majority of cases of AD are sporadic, they do not run in families...molecular genetic analyses suggest that there are likely many genes that influence one's susceptibility to AD (see p. 633, left column, 2nd paragraph). Additionally, Mattson indicates that although drugs can temporarily improve

memory, at present there are no treatments that can stop or reverse the inexorable neurodegenerative process (see abstract).

In regards to "a method for reducing the levels of Aβ peptide in a mammal", it is well known in the art that Aβ precursor protein (APP) can reside at neuron and glial cell surfaces or undergo proteolytic processing into secreted fragments (see for example, Perez et al, The Journal of Neuroscience, 1997, 17(24): 9407-9414 and Mattson MP, Nature, 2004, 430: 631-639). Mattson indicates that central to the disease is altered proteolytic processing of the APP resulting in the production and aggregation of neurotoxic forms of Aβ. Neurons that degenerate in AD exhibit increased oxidative damage, impaired energy metabolism and perturbed celluar calcium homeostasis (see p. 631, left column, last couple sentences from 1st paragraph). Further, Mattson indicates that APP is widely expressed in cells throughout the body where the amount produced is influenced by the developmental and physiological state of the cells (see p. 632, left column, 1st sentence of 1st paragraph). Aβ peptide is located at the cell surface with part of the peptide embedded in the membrane (see p. 632, left column, last part of 2nd sentence and Figure a on p. 632, right column). Further, Mattson indicates that the normal functions of APP are not fully understood, but increasing evidence suggests it has important roles in regulating neuronal survival, neurite outgrowth, synaptic plasticity and cell adhesion (see p. 632, left column, 1st sentence of 3rd paragraph). Mattson additionally indicates that the initial experiments showing that synthetic fragments of Aβ can kill cultured neurons led to a series of studies that have revealed the chemical and

cell biological bases for the synaptic dysfunction and death of neurons in AD (see, p. 632, right column, 1st sentence of 1st paragraph).

Schenk et al (Nature, 1999, 400: 173-177) indicates that transgenic mouse, which overexpresses mutant human APP (amino acid 717 is Phe instead of Val), progressively develops many of the neuropathological hallmarks of AD in an age- and brain-region-dependent manner (see p. 174, left column, 1st paragraph). Schenk et al investigated the effects of immunization against amyloid-plaque-related proteins on the development of AD-like neuropathology in young PDAPP mice and indicates that immunization with $A\beta_{42}$ resulted in almost complete prevention of amyloid-β deposition (see p. 174, right column, 1st sentence of 1st paragraph). Quantitative imaging of the amyloid-β burden in the hippocampus was utilized to verify the near-total reduction achieved in $A\beta_{42}$-treated animals (see p. 174, right column). Brain sections from $A\beta_{42}$-treated mice were immunostained with thioflavin S to rule out the possibility that the lack of immunohistochemically detectable plaques was due to competition by the de novo anti-Aβ antibodies produced by the animals (see p. 174, right column).

However, the prior arts do not describe how to measure the "reduced levels of Aβ peptide in a mammal". Mattson discloses that APP is widely expressed in cells throughout the body where the amount produced is influenced by the developmental and physiological state of the cells (see p. 632, left column, 1st sentence of 1st paragraph) and that the normal functions of APP are not fully understood, but increasing evidence suggests it has important roles in regulating neuronal survival, neurite outgrowth, synaptic plasticity and cell adhesion (see p. 632, left column, 1st sentence of

3rd paragraph). Since APP, which comprises the Aβ peptide, is being expressed throughout the body and plays important roles, it would be difficult to measure the amount of the peptide in a mammal. The prior arts investigate the plaque formation on the brains (see Mattson and Schenk), and most of the analyses were quantitative and looking at the cross sections of the brain.

Additionally, the Merck manual indicates that most cases are sporadic, with late onset and unclear etiology (see Merck manual, "Alzheimer's disease", Etiology and Pathophysiology). Since symptoms, signs are similar to those of other dementia, distinguishing Alzheimer's disease from other dementias is difficult (see Merck Manual, "Alzheimer's disease", Symptoms, Signs, and Diagnosis). And since art recognizes that there is no cure for AD, as indicated by Mattson (although drugs can temporarily improve memory, at present there are no treatments that can stop or reverse the inexorable neurodegenerative process).

The art provide guidance to how to measure the Aβ plaques on the brain, but do not provide guidance as how to measure the levels of Aβ peptides in mammals. However, none of the prior arts provide guidance as how to determine individuals who are susceptible to Alzheimer's disease.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Applicant's activity is based on the determination of predicting those who are susceptible to Alzheimer's disease. Since the activity is based on determining the patient population that is susceptible to Alzheimer's disease, the predictability in the art is low. This is due to the fact that the art has recognized the difficulty in determining the patient population who are susceptible to Alzheimer's disease.

The claims do not identify the patient population, therefore, the claims imply that anyone can be protected against Alzheimer's disease. Furthermore, since the claims do not identify the patient population, all of the Aβ peptide can be reduced from everybody. However, the Applicant has not shown who will be susceptible to Alzheimer's disease and the population who need reduction in Aβ peptide. There are too many variables between the experimentation, thus, it clearly shows the unpredictability of the art.

(5) The breadth of the claims:

The claims are drawn to a method for reducing the levels of Aβ peptide in a mammal and a method for preventing or treating a disease, disorder or condition associated with plaques of Aβ peptide in a mammal, comprising administering soluble Nogo receptor antagonist. The claims do not identify patient population, just mammals, so they imply that all mammals can be prevented from disease, disorder or condition associated with plaques of Aβ peptide, and the Aβ peptide is reduced from ALL mammals.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

Although the specification provides guidance on how to measure the Aβ plaque formation on the brain, the specification does not disclose how to measure the Aβ peptide level in mammals. Additionally, it is unclear as to when to administer the compound is to be administered and the patient population. The working examples are directed towards the brain tissue samples. Example 1 discloses looking at subcellular localization of NgR and Nogo in AD and control brain tissue samples. Example 1 discloses that subcellular localization of NgR and Nogo is altered in AD, and thus suggest that the NogoA/NgR pathway has a role in AD pathology (see. pp. 6-7). Example 2 discloses that APP and multiple forms of Aβ peptide interact with NgR and show that amino acids 7-28 are involved in NgR affinity and amino acids 15-28 are especially important (see p. 7 and paragraph [0064]). Example 4 discloses that NgR enhances Aβ production. The APPsw transgene from APPsw/PSEN-1(DeltaE9) mice was bred onto a NgR null background, and brain extracts were examined for Aβ and sAPPα levels at 3 months of age. The absence of NgR significantly reduced the production of both Aβ and sAPPα under physiologic conditions (see Example 4, paragraph [0067]). Further, the specification discloses that treatment with a NgR antagonist reduces Aβ plaque deposition (see Example 6). The example discloses sacrificing the mice and measuring the brain Aβ levels using an ELISA kit (see paragraph [0069]). Aβ deposition into amyloid plaques was assessed by anti-Aβ immunohistochemistry. As stated above, the specification does not disclose how to

measure the Aβ peptide levels in mammals. The working examples are limited to brain tissue and rat brain, and the animals to be sacrificed to measure the Aβ plaque levels in the brain.

In order to measure the peptide level, the peptide must be extracted somehow. Since Example 2 discloses that APP and multiple forms of Aβ peptide interact with NgR, and it is well known in the art that Aβ peptide is derived from proteolytic cleavage of APP protein, Aβ peptide is naturally occurring in the body. Measuring the any levels of Ab peptide would have to have some sort of starting point and an end point. Whether the Ab peptide is degraded by the NgR antagonist or is inhibited from being cleaved off from the APP protein, there must be a starting measurement of the initial Ab peptide to measure the reduced level of Ab peptide. Even if the Ab peptide level is reduced, unless the Ab peptide is excluded out in the urine or other bodily fluid, the Ab peptide, and any fragment thereof, would naturally be in the body. Therefore, the Invention is not enabled for measuring the reduced levels of Ab peptide in a mammal.

Claims 44 and 52-53 of instant application is drawn to disorder or condition is Alzheimer's disease. The Merck manual indicates Alzheimer's disease is chronic, global, usually irreversible deterioration of cognition. The main types of Alzheimer's disease are: vascular dementia, Lewy body dementia, frontal-temporal dementias, and HIV-associated dementia (See Merck manual, "Dementia", Etiology and Classification, 2nd paragraph). Furthermore, Alzheimer's disease causes progressive cognitive deterioration and is characterized by senile plaques, beta-amyloid deposits, and neurofibrillary tangles in the cerebral cortex and subcortical gray matter (see Merck

manual in Dementia under "Alzheimer's disease). Furthermore, the Merck manual indicates that most cases are sporadic, with late onset and unclear etiology (see Merck manual, "Alzheimer's disease", Etiology and Pathophysiology). Since symptoms, signs are similar to those of other dementia, distinguishing Alzheimer's disease from other dementias is difficult (see Merck Manual, "Alzheimer's disease", Symptoms, Signs, and Diagnosis).

Furthermore, Mattson MP (Nature, 2004, 430: 631-639) indicates that the risk of Alzheimer's disease (AD) dramatically increases in individuals beyond the age of 70 (see p. 631, left column, 1st sentence). The vast majority of cases of AD are sporadic, they do not run in families...molecular genetic analyses suggest that there are likely many genes that influence one's susceptibility to AD (see p. 633, left column, 2nd paragraph). Additionally, Mattson indicates that although drugs can temporarily improve memory, at present there are no treatments that can stop or reverse the inexorable neurodegenerative process (see abstract).

The specification has not provided guidance in the way of a disclosure to how to determine individuals that need protection against Alzheimer's disease and how to measure the level of Ab peptide in a mammal. There is no clear guidance as to how to determine the patient population, since APP exists in the body and a patient population is not defined, and it is unclear who would develop the AD, more guidance is necessary. Since the prior art is still unclear as to who are susceptible to AD, more guidance is necessary.

(8) The quantity of experimentation necessary:

Since it is uncertain to predict the patient population who are susceptible for Alzheimer's disease, and the Applicant have not provided the appropriate time frame at which the compound should be administered, and the Applicant have not provided guidance as how to measure the Aβ peptide in a mammal, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the NgR antagonist would be effective in protecting a mammal against AD and in reducing the levels of Aβ peptide in a mammal.

Please note that the term "prevent" in an absolute definition which means to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic" or "treat" or "alleviate", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes)- including preventing such disorders as Alzheimer's disease, which is clearly not recognized in the medical art as being totally preventable condition.

Rejection-35 U.S.C. 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 42-45, 47, 51-54, 56 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Barske et al (WO 03/018631).

19. The instant claims are drawn to a method for reducing the levels of Ab peptide in a mammal, comprising administering a therapeutically effective amount of a soluble Nogo receptor antagonist and a method of preventing or treating a disease, disorder or condition associated with plaques of Ab peptide in a mammal, comprising administering a therapeutically effective amount of a soluble Nogo receptor polypeptide, wherein the disease, disorder or condition is Alzheimer's Disease (AD).

20. Barske et al teach polypeptides and polynucleotides that encode proteins of the Nogo-66 receptor (NgR) family. Further, the reference teaches their use in identifying compounds that may be agonists or antagonists that are potentially useful in regeneration and protection of the nervous system, and to production of NgRH2 polypeptides, derivatives and antibodies (see abstract). This reads on claim 42. The reference further teaches that a NgR antagonist peptide, comprising the N-terminal 40 amino acids of Nogo-66 was shown to induce regeneration in spinal cord injury and also improved functional recovery, providing a potential therapeutic for CNS injuries (see p. 2, lines 17-20). This reads on claims 47, 56, and 60. Furthermore, the reference teaches methods for treatment of diseases, disorders or damage which ultimately results in damage of the nervous system in a subject, where the disease is mediated by or associated with an increase or decrease in NgRH2 gene expression...such diseases, disorders or damage include CNS trauma, infarction...degenerative nerve diseases (including but not limited to Alzheimer's disease, Parkinson's disease, Huntington's

Chorea, multiple sclerosis...) (see p. 4, lines 24-33), and can be achieved by administering compounds that interfere with NgRH2 activity (see p. 5, lines 1-2). This reads on claims 43, 44, 52 and 53. The reference teaches that the preferred polypeptides and polynucleotides are expected to have, inter alia, similar biological functions/properties to their homologous polypeptides and polynucleotides. Furthermore, the polypeptides and polynucleotides have at least one activity of human or rat NgRH2 (see p. 12, lines 32-33 and p. 13, lines 1-2). The reference further teaches that for any compounds, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models (dogs, rabbits, dogs, or pigs), and the appropriate concentration ranges and route of administration can be determined...a therapeutically effective dose refers to that amount of active ingredient, for example, antibodies, agonists, antagonists or inhibitors of NgRH2, which ameliorates the symptoms or conditions (see p. 21, lines 14-20). This reads on "therapeutically effective amount" of claims 42, 51 and 60. Furthermore, the pharmaceutical composition may be provided as a salt and can be formed with many acids...salts tend to be more soluble in aqueous or other protonic solvents (see p. 21, lines 7-9). This further reads on claims 42, 47, 56 and 60. Furthermore, the reference teaches that the pharmaceutical composition may be administered by any number of routes including, oral, intravenous, intramuscular, intra-articular, intra-arterial, intramedullary, intrathecal, intraventicular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical sublingual, or rectal means (see p. 20, lines 30-33). This reads on claims 45 and 54, since bolus injections or infusions are considered to be

given as intravenous injections. Therefore, the prior art reads on claims 42-45, 47, 51-54, 56 and 60. The reference is silent as to the reducing the levels of Aβ peptide in a mammal. However, since the prior art teaches the method for treating AD utilizing the NgRH2 peptide antagonist, and has similar biological functions/properties to their homologous polypeptides, it would inherently reduce the levels of Aβ peptide once administered to the mammal.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

21. Claims 42, 47, 49 and 58 are rejected under 35 U.S.C. 102(e) as being anticipated by Baker et al (US Patent # 7029874).

22. The instant claims are drawn to a method for reducing the levels of Ab peptide in a mammal comprising administering a therapeutically effective amount of a soluble Nogo receptor antagonist comprises of SEQ ID NO: 3.

23. Baker et al teach polypeptides and nucleic acid molecules encoding those polypeptide (see abstract). The reference teaches SEQ ID NO: 400 (see SEQ ID NO: 400 enclosed) that comprises the SEQ ID NO:3. Since SEQ ID NO: 400 comprises SEQ ID NO:3, it inherently has the polypeptide functionality and activity. This reads on claims 42, 49 and 58. The reference further teaches that neurotrimin as well as other members of the IgLON subfamily have been identified to have effect upon neural patterning, differentiation, maturation and growth. Thus, PRO337, the human neurotrimin homolog would be expected to have utility in disease which are characterized by neural

disfunction...can be used to treat human neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, Huntington's Chorea, Down's Syndrome, nerve deafness, and Meniere's disease (see column 212, lines 14-30). Further, the reference teaches that PRO polypeptides may also be employed as therapeutic agents (see column 191, lines 20-21) and the route of administration is for example injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration or by sustained release systems (see column 191, lines 53-57). Furthermore, the reference teaches when in vivo administration of a PRO polypeptide or agonist or antagonist thereof is employed, normal dosage amounts may vary from about 10 ng/kg to up to 100 mg/kg of mammal body weight or more per day, preferably about 1mg/kg/day to 10 mg/kg/day, depending upon the route of administration (see column 192, lines 3-8). This reads on the therapeutically effective amount of the antagonist limitation. The reference is silent as to the reducing the levels of Aβ peptide in a mammal. However, since the prior art teaches that the polypeptides can be used to treat Alzheimer's disease, and the human neurotrimin homolog would be expected to have utility in disease which are characterized by neural disfunction (such as AD), it would inherently reduce the levels of Aβ peptide once administered to the mammal. Therefore, the prior art reads on claims 42, 47, 49 and 58.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

24. Claims 42, 47, 49 and 58 are rejected under 35 U.S.C. 102(a) as being anticipated by Baker et al (US Patent # 7029874).

25. The instant claims are drawn to a method for reducing the levels of Ab peptide in a mammal comprising administering a therapeutically effective amount of a soluble Nogo receptor antagonist comprises of SEQ ID NO: 3.

26. Baker et al teach polypeptides and nucleic acid molecules encoding those polypeptide (see abstract). The reference teaches SEQ ID NO: 400 (see SEQ ID NO: 400 enclosed) that comprises the SEQ ID NO:3. Since SEQ ID NO: 400 comprises SEQ ID NO:3, it inherently has the polypeptide functionality and activity. This reads on claims 42, 49 and 58. The reference further teaches that neurotrimin as well as other members of the IgLON subfamily have been identified to have effect upon neural patterning, differentiation, maturation and growth. Thus, PRO337, the human neurotrimin homolog would be expected to have utility in disease which are characterized by neural disfunction...can be used to treat human neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, Huntington's Chorea, Down's Syndrome, nerve deafness, and Meniere's disease (see column 212, lines 14-30). Further, the reference teaches that PRO polypeptides may also be employed as therapeutic agents (see column 191, lines 20-21) and the route of administration is for example injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration or by sustained release systems (see column 191, lines 53-57).

Furthermore, the reference teaches when in vivo administration of a PRO polypeptide or agonist or antagonist thereof is employed, normal dosage amounts may vary from about 10 ng/kg to up to 100 mg/kg of mammal body weight or more per day, preferably about 1mg/kg/day to 10 mg/kg/day, depending upon the route of administration (see column 192, lines 3-8). This reads on the therapeutically effective amount of the antagonist limitation. The reference is silent as to the reducing the levels of Aβ peptide in a mammal. However, since the prior art teaches that the polypeptides can be used to treat Alzheimer's disease, and the human neurotrimin homolog would be expected to have utility in disease which are characterized by neural disfunction (such as AD), it would inherently reduce the levels of Aβ peptide once administered to the mammal. Therefore, the prior art reads on claims 42, 47, 49 and 58.

Conclusion

27. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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